

## Ethylene Glycol Ethers (EGME, EGEE, EGMEA, EGEEA)

### I. Physical and Chemical Properties

#### *Ethylene glycol ethyl ether (EGEE; 2-ethoxyethanol)*

|                                     |   |
|-------------------------------------|---|
| <i>CAS Registry Number</i>          | 110-80-5                                      |
| <i>Description</i>                  | Colorless liquid                              |
| <i>Molecular formula</i>            | $C_4H_{10}O_2$                                |
| <i>Molecular weight</i>             | 90.12 g/mol                                   |
| <i>Air concentration conversion</i> | 3.69 $\mu\text{g}/\text{m}^3$ per ppb at 25°C |

#### *Ethylene glycol ethyl ether acetate (EGEEA; 2-ethoxyethanol acetate)*

|                                     |   |
|-------------------------------------|---|
| <i>CAS Registry Number</i>          | 111-15-9                                      |
| <i>Description</i>                  | Colorless liquid                              |
| <i>Molecular formula</i>            | $C_6H_{12}O_3$                                |
| <i>Molecular weight</i>             | 132.16 g/mol                                  |
| <i>Air concentration conversion</i> | 5.41 $\mu\text{g}/\text{m}^3$ per ppb at 25°C |

#### *Ethylene glycol methyl ether (EGME; 2-methoxyethanol)*

|                                     |  |
|-------------------------------------|--|
| <i>CAS Registry Number</i>          | 109-86-4                                     |
| <i>Description</i>                  | Colorless liquid                             |
| <i>Molecular formula</i>            | $C_3H_8O_2$                                  |
| <i>Molecular weight</i>             | 76.09 g/mol                                  |
| <i>Air concentration conversion</i> | 3.1 $\mu\text{g}/\text{m}^3$ per ppb at 25°C |

#### *Ethylene glycol methyl ether acetate (EGMEA; 2-methoxyethanol acetate)*

|                                     |   |
|-------------------------------------|---|
| <i>CAS Registry Number</i>          | 110-49-6                                      |
| <i>Description</i>                  | Colorless liquid                              |
| <i>Molecular formula</i>            | $C_5H_{10}O_3$                                |
| <i>Molecular weight</i>             | 118.3 g/mol                                   |
| <i>Air concentration conversion</i> | 4.83 $\mu\text{g}/\text{m}^3$ per ppb at 25°C |

### II. Overview

Developmental toxicity is one of the key toxicological endpoints of concern for impacts on infants and children. The developing fetus is susceptible to certain glycol ethers and their acetates. These are ethylene glycol ethers with alkyl chains of one or two carbon atoms: EGME, EGMEA, EGEE, and EGEEA. The developing fetus appears to be susceptible at levels lower than those associated with maternal toxicity. The effects of EGME, EGEE, and their acetates are considered severe because they include teratogenicity, testicular toxicity, and fetotoxicity in rabbits.

Bolt and Golka (1990) report that a woman, who was exposed occupationally to EGMEA, bore in successive pregnancies two sons with penile hypospadias. Recent epidemiologic studies from Europe suggest an association of major congenital malformations with exposure to glycol ethers during the first trimester of pregnancy.

These chemicals are fetotoxic and teratogenic in animals. Pregnant animals exposed during development to either EGEE or EGME by inhalation had more malformed or dead fetuses than unexposed controls (Tinston *et al.*, 1983a; Doe, 1984; Hanley *et al.*, 1984). Inhaled EGME and EGEE tend to cause skeletal anomalies and developmental neurotoxicity at exposure concentrations below those causing toxicity to mature animals. EGEE, EGEEA, EGME, and EGMEA appear to be more toxic to the developing human than to humans at later stages of life. Therefore, EGEE and EGME (and their acetates) are considered priority chemicals for evaluation of potential differential effects on infants and children.

It is difficult to estimate the magnitude of risk that would occur at concentrations typical of California urban ambient air, since no monitoring data are available. Point source emissions of total glycol ethers for the facilities reporting emissions under the Air Toxics Hot Spots Program appear to be substantial (Table 1 below). These include significant amounts of ethylene glycol ethyl ethers. Data are not readily available to determine to what extent the emissions of unspecified glycol ethers represent methyl or ethyl ethers or their acetates.

### III. Principal Sources of Exposure

Table 1. Air Toxics Hot Spots Emissions of Various and Total Glycol Ethers

| Glycol ether                  | California emissions | Ambient air levels | SCAQMD        |
|-------------------------------|----------------------|--------------------|---------------|
| EGEE                          | 443,748 pounds       | Not monitored      | Not monitored |
| EGEEA                         | 66,851 pounds        | Not monitored      | Not monitored |
| EGME                          | 7,398 pounds         | Not monitored      | Not monitored |
| EGMEA                         | 3,060 pounds         | Not monitored      | Not monitored |
| Glycol ethers (not speciated) | 2,922,744 pounds     | Not monitored      | Not monitored |

**EGEE.** Ethylene glycol monoethyl ether is a widely used solvent for nitrocellulose, dyes, inks, resins, lacquers, paints, and varnishes. EGEE is also a component of many cleaning agents, epoxy coatings, paints, hydraulic fluid, and is an anti-icing fuel additive in aviation. EGEE is also a chemical intermediate in the production of another solvent, ethylene glycol monoethyl ether acetate (EGEEA). The specific annual statewide industrial emissions of EGEE from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 443,748 pounds (CARB, 2000), plus some proportion of the non-speciated glycol ethers.

**EGEEA.** Ethylene glycol monoethyl ether acetate is used in automobile lacquers where it retards "blushing" and evaporation and imparts a high gloss (HSDB, 1996). It is also used as a solvent for nitrocellulose, oils, and resins and as a component of varnish removers and wood stains. EGEEA is

also used in the treatment of textiles and leather. The annual specific statewide industrial emissions of EGEEA from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 66,851 pounds (CARB, 2000).

**EGME.** Ethylene glycol monomethyl ether (EGME) is used as a solvent for cellulose acetate and resins as well as a solvent in the semiconductor industry. It is also used in dyeing leather and in the manufacture of photographic film. EGME is used as an anti-freeze in jet fuels. Quick drying varnishes, enamels, nail polishes, and wood stains may also contain EGME. The specific annual statewide industrial emissions of EGME from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 7398 pounds (CARB, 2000), plus some proportion of the non-speciated glycol ethers.

**EGMEA.** Ethylene glycol monomethyl ether acetate is used as a solvent for nitrocellulose, cellulose acetate, and various other gums, resins, waxes, and oils. It is also used in the semiconductor industry and in textile printing, photographic films, lacquers, and silk-screening inks. The annual specific statewide industrial emissions of EGMEA from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 3,060 pounds (CARB, 2000).

The Air Resources Board does not monitor routinely for glycol ethers. Much of the emissions of glycol ethers (nearly 3 million pounds) is not speciated, so we do not know how much additional toxic ethylene glycol ethers are emitted. The concern for exposure is in the vicinity of specific facilities that emit large amounts of these ethylene glycol ethers (Hot Spots) and produce high concentrations in the local area.

#### **IV. Potential for Differential Effects**

##### **A. Summary of the Key Human Studies**

Congenital malformations may be induced in humans. In a case report Bolt and Golka (1990) describe a woman, exposed occupationally to EGMEA during pregnancy, who bore sons with penile hypospadias in successive pregnancies. Saavedra *et al.* (1997) described facial malformations and varying degrees of mental retardation in 44 offspring of mothers who were exposed occupationally to EGME and ethylene glycol at the factory of an American company producing capacitors in Mexico.

Using 6 registers in the European Registration of Congenital Anomalies (EUROCAT), a large group of investigators studied major congenital malformations reported between 1989 and 1992 (Ha *et al.*, 1996; Cordier *et al.*, 1997; Lorente *et al.*, 2000). Preliminary results (Ha *et al.*, 1996) among mothers who were working during pregnancy found excesses of oral clefts (OR = 2.0; 95% CI = 1.1-4.1), central nervous system malformations (OR = 1.8; 95% CI = 1.1-3.3), and musculoskeletal malformations (OR 1.6; 95% CI = 0.9-2.8) among glycol ether exposed mothers. However, only one mother was exposed to "group I glycol ethers" (a classification defined in the report as EGME, EGMEA, EGEE, EGEEA, "and some polyethylenic compounds").

More definitive results were reported by Cordier *et al.* (1997). The entire study comprised 984 cases with major congenital malformations and 1,134 matched controls. After adjustment for several potential

confounding exposures (other solvents, anesthetic gases, pesticides, lead), the overall odds ratio (OR) of congenital malformation associated with glycol ether exposure was 1.44 [95% CI = 1.10-1.90]. This OR was based on the exposure to glycol ethers of 158 of the 648 cases occurring among mothers who worked during the first trimester. The association with exposure to glycol ethers appeared particularly strong for neural tube defects (94 cases, 28 exposed to glycol ethers, OR = 1.94; 95% CI = 1.16-3.24), multiple anomalies (114 cases, 34 exposed, OR = 2.00; 95% CI = 1.24-3.23), and cleft lip (64 cases, 23 exposed, OR = 2.03; 95% CI = 1.11-3.73). However, this study did not discuss sub-grouping of glycol ethers.

The relationship between occupational exposures of 851 women (100 mothers of babies with orofacial clefts and 751 mothers of healthy referents) who worked during the first trimester of pregnancy and orofacial clefts (Lorente *et al.*, 2000) was evaluated. This analysis suggested that occupational exposure to glycol ethers was associated with orofacial clefts (OR 1.7, 95% CI 0.9-3.3 for cleft lip with or without cleft palate).

EGME is metabolized by an alcohol dehydrogenase to methoxyacetaldehyde, which is then metabolized by aldehyde dehydrogenase to methoxyacetic acid. EGEE is metabolized to ethoxyacetaldehyde, then to ethoxyacetic acid. The alkoxyacids are considered to be more toxic than their parent glycol ethers. EGMEA and EGEEA are hydrolyzed to acetate and the respective ethylene glycol ethers, which are then dehydrogenated.

### **B. Summary of the Key Animal Studies**

**EGEE.** Exposure to EGEE induces malformations in offspring in the absence of significant maternal toxicity. Nelson *et al.* (1981) reported changes in brain chemistry in the offspring of Sprague-Dawley rats (n=14-15) exposed to 100 ppm (369 mg/m<sup>3</sup>) EGEE for 7 h/day on gestational days (gd) 7-13 or 14-20. The only effect observed in the dams was slightly prolonged gestation in those exposed on gd 14-20 (p < 0.001). Six neurobehavioral tests were used to assess CNS functioning at various stages of development. In the pups exposed during gd 7-13, a decreased rotorod speed and an increased latency period for leaving the central area of an open field were observed. The activity of the offspring of rats exposed during gd 14-20 decreased on the activity wheel, and avoidance conditioning, begun on day 60 of age, revealed that these pups received an increased number and duration of shocks. Whole brain norepinephrine levels in the newborns of the exposed dams from both exposure groups (7-13 and 14-20 days) decreased. At age 21 days, norepinephrine was increased in the cerebrum, brain stem and midbrain of 7- to 13-day exposed pups only. Increased dopamine levels were found in the cerebrum only of pups from both exposure periods, while serotonin was increased in the 14-20 day exposure group. The midbrains of pups exposed on gd 7-13 had protein levels that exceeded the controls. (Gross teratogenic anomalies (terata) were not detected in this study, possibly due to either insufficient numbers of animals or inadequate procedures.)

Specific skeletal defects were reported in the progeny of pregnant rats exposed to 10, 50, and 250 ppm (40, 200, and 920 mg/m<sup>3</sup>) EGEE 6 hours per day on days 6-15 of gestation (Tinston *et al.*, 1983a). Maternal toxicity, as indicated by reduced hemoglobin, hematocrit, and mean cell volume in

red blood cells, was observed in rats exposed to 250 ppm EGEE. A significant reduction in the number of live fetuses was observed in rats exposed to 10 and 250 ppm, and a reduction in total litter weight was observed in rats exposed to 10 ppm and 50 ppm. Intergroup comparison showed significantly increased incidence of total minor skeletal defects in fetuses in the 250 ppm dose group; delayed ossification was the most common abnormality observed at this dose. Specific skeletal defects, including delayed ossification of the cervical vertebrae and sternebrae and the presence of extra ribs, were significantly increased in not only the 250 ppm dose group but also in the 50 ppm dose group where there was no apparent maternal toxicity.

**EGEEA.** EGEEA is fetotoxic and teratogenic at concentrations below that necessary to induce maternal toxicity. Pregnant rabbits (24 or 25/group) were exposed to 0, 25, 100, or 400 ppm EGEEA by inhalation for 6 hours/day on gd 6-18 (Tinston *et al.*, 1983b; reviewed in Doe, 1984) and were killed on gd 29. Maternal effects (decreased weight gain, decreased food consumption, decreased hemoglobin) were observed at 400 ppm. The number of rabbits with total fetal resorptions was increased in the 400 ppm dose group, accompanied by a decrease in weight in surviving fetuses. A reduction in average fetal weight was also observed at 100 ppm EGEEA, but this effect may relate to the increased litter size among dams in this dose group. Evidence of teratogenicity was observed in the 400 ppm dose group, with increased major malformations of the vertebral column. Both 400 and 100 ppm EGEEA were found to be fetotoxic as indicated by retarded ossification. No statistically significant effects were observed in the 25 ppm dose group. (A single case of a major defect (kidney agenesis) was observed in both the 25 and 400 ppm EGEEA dose groups.)

**EGME.** EGME is fetotoxic and teratogenic at concentrations below that necessary to induce maternal toxicity. Hanley *et al.* (1984) exposed pregnant rats and rabbits to 3, 10, or 50 ppm (9.6, 32, or 160 mg/m<sup>3</sup>) EGME for 6 hours per day on gd 6-15 (rats) or gd 6-18 (rabbits). Pregnant mice were exposed to 10 or 50 ppm (32 or 160 mg/m<sup>3</sup>) EGME for 6 hours per day on gd 6-15. Transient decreases in maternal body weight gain among rats, mice, and rabbits exposed to 50 ppm were the only consistent signs of maternal effects. A statistically significant increase in the incidence of skeletal variations was observed in rats and mice following maternal exposure to 50 ppm EGME. Gross soft tissue (cardiovascular) and skeletal teratogenic effects and significantly decreased fetal body weights were observed in rabbits following maternal exposure to 50 ppm EGME. In rabbits, a significant increase in the rate of fetal resorption was observed in the 10 ppm exposure group (Table 2). Thus 10 ppm was considered a LOAEL for increased resorptions and 3 ppm a NOAEL. Although the authors attribute the statistical significance of this effect to an unusually low rate of resorptions in controls compared to historical controls, historical control data were not presented.

Table 2. EGME Rabbit Teratology: Selected Observations from Hanley et al. (1984)

|                          | 0 ppm        | 3 ppm        | 10 ppm        | 50 ppm                    |
|--------------------------|--------------|--------------|---------------|---------------------------|
| No. litters              | 23           | 24           | 24            | 24                        |
| Live fetuses/litter      | 8 ± 2        | 7 ± 3        | 8 ± 3         | 6 ± 3                     |
| Implantations resorbed   | 4% (7/180)   | 8% (14/186)  | 11% (23/210)* | 24% (46/191)*             |
| Litters with resorptions | 22% (5/23)   | 42% (10/24)  | 58% (14/24)*  | 67% (16/24)*              |
| Fetal bw (g)             | 39.57 ± 5.48 | 39.13 ± 6.24 | 38.83 ± 4.54  | 35.88 ± 3.79*             |
| Limb defects             | 0            | 1 fetus      | 1 fetus       | 55 fetuses in 16 litters* |
| Cardiovascular defects   | 0            | 0            | 0             | 34 fetuses in 15 litters* |

\* p<0.05 vs. the control value

EGME may cause changes in brain chemistry when exposure occurs during development. Nelson *et al.* (1984) exposed 18 Sprague-Dawley male rats to 25 ppm EGME (78 mg/m<sup>3</sup>) 7 hours/day, 7 days/week for 6 weeks prior to mating with unexposed females. The brains of 21-day-old offspring had neurochemical changes, especially in the brainstem and cerebrum (e.g., dopamine, norepinephrine). They showed no behavioral effects as indicated by neuromotor function, activity, and simple learning ability. The offspring of pregnant females (15 animals/group) in both groups exposed to 25 ppm EGME during either gestation days 7-13 (group 1) or 14-20 (group 2) had similar neurochemical changes (e.g., decreased levels of acetylcholine and increased levels of cerebral dopamine at 21 days post-partum). There was a significant difference in avoidance conditioning in the offspring of the group exposed during gestation days 7-13. The concentration of 25 ppm is a LOAEL for developmental toxicity in this study.

## V. Additional Information

### A. Other Toxicity

EGEE, and EGME and their respective alkoxy metabolites all cause toxicity to 9.5-day-old rat embryos cultured in vitro. Based on a comparison done with this assay the potency for teratogenicity for the ethylene glycol ethers (and for their alkoxyacid metabolites) is EGME > EGEE > EGPE (ethylene glycol propyl ether) > EGBE (ethylene glycol butyl ether) or the shorter the chain, the greater the potency (Rawlings *et al.*, 1985)

The glycol ethers cause damage to the developing fetus at exposure levels below those that cause maternal toxicity. Toxicity to the bone marrow and thymus at higher doses in adult animals indicate the possibility of enhanced risk to developing hematopoietic and immune systems.

### B. Regulatory Background

EGME, EGMEA, EGEE, and EGEEA are federal hazardous air pollutants (HAPs) and were identified as toxic air contaminants (TACs) in California in April 1993 under AB 2728. The acute and chronic

RELs are tabulated below (Table 3). The 4 chemicals are listed under Proposition 65 as developmental toxicants and as male reproductive toxicants.

Table 3. OEHHA Health Guidance Values and Proposition 65 Status

| Glycol ether | Acute REL   | Chronic REL                              | Cancer Potency | Prop 65                               |
|--------------|---|--|----------------|---------------------------------------|
| EGEE         | 370 $\mu\text{g}/\text{m}^3$<br>(100 ppb)<br>(6 h avg time) | 70 $\mu\text{g}/\text{m}^3$<br>(20 ppb)  | None           | Developmental and male repro toxicant |
| EGEEA        | 140 $\mu\text{g}/\text{m}^3$<br>(25 ppb)<br>(6 h avg time)  | 300 $\mu\text{g}/\text{m}^3$<br>(60 ppb) | None           | Developmental and male repro toxicant |
| EGME         | 93 $\mu\text{g}/\text{m}^3$<br>(30 ppb)<br>(6 h avg time)   | 60 $\mu\text{g}/\text{m}^3$<br>(20 ppb)  | None           | Developmental and male repro toxicant |
| EGMEA        | None  | 90 $\mu\text{g}/\text{m}^3$<br>(20 ppb)  | None           | Developmental and male repro toxicant |

### C. Description of RELs

**EGEE.** The acute REL for EGEE of 370  $\mu\text{g}/\text{m}^3$  (OEHHA, 1999) is based on specific skeletal defects, including delayed ossification of the cervical vertebrae and sternbrae and extra ribs, seen in the fetuses from pregnant rats exposed by inhalation 6 hours per day on days 6-15 of gestation (Tinston *et al.*, 1983a; Doe, 1984). The chronic REL for EGEE of 70  $\mu\text{g}/\text{m}^3$  (OEHHA, 2000) is based on testicular degeneration and decreased hemoglobin in rabbits as reported by Barbee *et al.* (1984).

**EGEEA.** The acute REL for EGEEA of 140  $\mu\text{g}/\text{m}^3$  (OEHHA, 1999) is based on teratogenicity and fetotoxicity in rabbits as determined by Tinston *et al.* (1983b). The chronic REL for EGEEA of 300  $\mu\text{g}/\text{m}^3$  (OEHHA, 2000) is based on the same study.

**EGME and EGMEA.** The acute REL for EGME of 93  $\mu\text{g}/\text{m}^3$  (OEHHA, 1999) is based on teratogenic effects in rabbits as reported by Hanley *et al.* (1984). The chronic REL for EGME of 60  $\mu\text{g}/\text{m}^3$  (OEHHA, 2000) is based on testicular toxicity (reproductive system) in rabbits as determined by Miller *et al.* (1983). The chronic REL for EGMEA of 90  $\mu\text{g}/\text{m}^3$  (OEHHA, 2000) is also based on the Miller *et al.* study.

The most sensitive toxic endpoints associated with EGEE, EGEEA, EGME, and EGMEA are developmental toxicity and male reproductive toxicity. These glycol ethers appear to be more toxic to the developing human than to humans at later stages of life. However, based on current risk assessment methodology, the existing health criteria for glycol ethers should be adequately protective of children because they are based on developmental endpoints in animals. The lowest developmental NOAEL reported is 3 ppm for EGME and the acute REL of 30 ppb is 100-fold lower than the lowest NOAEL while the chronic REL of 20 ppb is 150-fold lower.

## **VI. Conclusions**

There is evidence in both humans and animals that exposure to specific glycol ethers can result in developmental toxicity. Developmental toxicity is one of the endpoints of concern for impacts on infants and children. Exposures to glycol ethers are not well characterized, but may occur near sources of industrial emissions. Thus, glycol ethers have been placed in Tier 2. Should evidence become available that exposures to glycol ethers, especially EGEE and EGME and their acetates, are significant near emissions sources, OEHHA may consider listing glycol ethers in a future update.

## **VII. References**

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